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Preliminary Evidence for Increased Frontosubcortical Activation on a Motor Impulsivity Task in Mixed Episode Bipolar Disorder

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Abstract

Background—Of all mood states, patients in mixed episodes of bipolar disorder are at the greatest risk for impulsive behaviors including attempted suicide. The aim of this study was to examine whether the neural correlates of motor impulsivity are distinct in patients with mixed mania.

Methods—Ten patients with bipolar disorder in a mixed episode (BP-M), 10 bipolar comparison participants in a depressed episode (BP-D), and 10 healthy comparison (HC) participants underwent functional MRI while performing a Go/No-Go task of motor impulsivity.

Results—Both patient groups had elevated, self-rated motor impulsiveness scores. The BP-M group also had a trend-level increase in commission errors relative to the HC group on the Go/No-Go task. While the full sample strongly activated a ventrolateral prefrontal-subcortical brain network, the BP-M group activated the amygdala and frontal cortex more strongly than the HC group, and the thalamus, cerebellum, and frontal cortex more strongly than the BP-D group.

Limitations—This study is primarily limited by a relatively small sample size.

Conclusions—Higher commission error rates on the Go/No-Go task suggest increased vulnerability to impulsive responding during mixed episodes of bipolar disorder. Moreover, the distinct pattern of increased brain activation during mixed mania may indicate a connection

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Conflict of Interest Dr. Strakowski served as a consultant to Pfizer and Consensus Medical Communications, and spoke for Adamed and CME Outfitters. Dr. Adler served as a speaker for Johnson & Johnson and Schering Plough/Merck. Dr. DelBello served as a speaker or consultant for Eli Lilly, Schering Plough/Merck, and Bristol-Myers Squibb. No other investigators have any financial relationships to report. The investigators have also received research grants from AstraZeneca, Eli Lilly, Johnson & Johnson, Shire, Janssen, Pfizer, Bristol-Myers Squibb, Repligen, Martek, Somerset, NARSAD, and GlaxoSmithKline for other projects. Although given the nature of this report, we do not believe any of these relationships represent conflicts with the data and results reported, we provide them in the spirit of full disclosure.

Contributors Drs. Fleck and Kotwal designed the study and wrote the protocol and first draft of the manuscript. They were also primarily responsible for the statistical analysis. Drs. Eliassen, Cerullo, and Lamy assisted in designing the imaging protocol and conducting various aspects of the first-level image analysis. Drs. Delbello, Adler, and Strakowski assisted in clinical aspects of the study including patient recruitment, diagnosis, and safety. Ms. Durling was the research coordinator responsible for the day-to-day operation of the study and image preprocessing. All authors contributed to and have approved the final manuscript.

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between behavioral impulsivity and a failure of neurophysiological “inhibition,” especially in the amygdala.

Keywords

impulsivity; bipolar disorder; mixed mania; fMRI; go/no-go task

Introduction

Bipolar disorder (BD) is characterized by impulse control problems. Clinical studies have identified poor impulse control as a factor associated with greater risk-taking, including attempted suicide, in BD (Michaelis et al., 2004). The occurrence of manic symptoms during depressive episodes is associated with even greater impulsivity and a higher probability of suicide attempts (Swann et al., 2007). This suggests that manic symptoms may provide the catalyst to act impulsively on negative thoughts during depression. Therefore, a better understanding of the neurological underpinnings of poor impulse control in mixed relative to depressed episodes of BD is an important empirical goal.

Impulsiveness is reported following damage to the orbitofrontal cortex (OFC) or ventrolateral prefrontal cortex (VLPFC), and practical and social judgment problems are also observed (Eslinger, 1999; Grafman et al., 1996). Lesions of prefrontal cortex can disrupt the ability to be guided by the future consequences of one's actions leading to poor decisions, presumably by “disconnecting” frontal monitoring systems from limbic input. Abnormalities within prefrontal-subcortical brain circuits also result in motor disruption, especially when the basal ganglia are involved (Lichter and Cummings, 2001).

Motor impulsivity tasks, such as Go/No-Go tasks, have been used extensively in the behavioral assessment of both higher-order frontal lobe and subcortical motor functions. Functional magnetic resonance imaging (fMRI) studies of acutely manic patients with BD have generally demonstrated decreased activation in VLPFC on non-emotional Go/No-Go tasks (Altshuler et al., 2005; Mazzola-Pomietto et al., 2009) and on non-emotional contrasts within affective Go/No-Go tasks (Elliot et al., 2004). However, to our knowledge, fMRI has not been used to examine motor impulsivity in mixed episodes of BD.

With these considerations in mind, we compared the neurophysiological response on a Go/No-Go motor inhibition task in patients with mixed mania to that of healthy and psychiatric control participants. We assessed neurofunctional variations within a VLPFC-subcortical emotional network previously implicated in BD (Strakowski et al., 2005; Strakowski et al., in press) using both exploratory voxel-wise and hypothesis driven region-of-interest (ROI) analyses. We predicted that relative to both healthy and bipolar depressed comparison groups, bipolar mixed participants would demonstrate (a) greater motor impulsivity on a Go/No-Go task, and (b) abnormal activation within the VLPFC-subcortical network.

Methods

Subjects

Ten adults with bipolar I disorder in a current mixed episode (BP-M) were the focus of this study and 10 adults with bipolar I disorder in a current depressed episode (BP-D) served as a patient comparison group. All patients were recruited from the inpatient psychiatry units at the University Hospital. Ten demographically matched healthy comparison (HC group) participants without any history of Axis-I psychiatric disorders in themselves or first-degree relatives were also recruited.

All participants were diagnosed using the Structured Interview for DSM-IV Axis I Disorders Patient edition (SCID-I/P) (First et al., 1995) administered by trained clinicians with established interrater reliability ($\kappa \geq 0.90$) (Strakowski et al., 2000). Inclusion criteria included a DSM-IV diagnosis of BD, current episode depressed with a Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) score ≥ 20 and Young Mania Rating Scale (YMRS) (Young et al., 1978) score ≤ 7 , or current episode mixed with a MADRS score ≥ 20 and YMRS score ≥ 20 . Exclusion criteria included an active medical condition or neurological illness, history of loss of consciousness >5 min, any DSM-IV substance use disorder not in sustained full remission or significant substance use during the week prior to testing, any contraindication to MRI scanning, left-handedness, and $IQ < 85$.

Two BP-M participants were excluded from analysis because they were later determined by expert consensus to be in a current manic episode ($n=1$) or moved excessively during scanning ($n=1$). Of the remaining 18 patient participants, 15 received psychotropic medications in the week prior to testing and three (one mixed and two depressed) did not. All participants provided written informed consent and were reimbursed for their participation. This study was approved by the Institutional Review Board of the University of Cincinnati.

Go/No-Go task

After collecting demographic/clinical data, participants were administered a practice session with the Go/No-Go task in the MRI control room. The Go/No-Go task was designed using E-Prime software. The essential feature of the task is the separation of frequent 'go' trials, which set up a prepotent motor response chain, and infrequent 'no-go' trials, for which inhibition of the prepotent motor response is required. The Go/No-Go task in this study consisted of letters presented on a computer screen for 500 msec each. A random inter-stimulus interval of 100-500 msec at 100 msec intervals was employed to "jitter" the stimuli for subsequent event-related image analysis. Stimuli were presented to the center of the visual field using nonferromagnetic goggles that provide a 30° field-of-view and obscure the peripheral field-of-view. Responses were obtained using a MRI-compatible button box. Participants were instructed to respond as quickly and accurately as possible with a button press using the thumb of their right hand to any letter presented, except letter 'V'. The first 30 trials were all 'go trials' to set up the pre-potent response. Subsequently there were 288 random trials of which 48 were 'V' trials (16.66%). The final 30 trials were constructed identical to the first 30, i.e., included no 'V' stimuli, in order to assess scanner drift. Number of correct hits, correct rejections, commission errors, omission errors, and hit reaction time (RT) were recorded. Total task duration was 4.64 minutes.

Image acquisition and preprocessing

All participants were scanned at the University of Cincinnati College of Medicine Center for Imaging Research using a 4.0 Tesla Varian Unity INOVA Whole Body MRI/MRS system. Participants reclined in supine position on the scanner bed and a radio-frequency coil was placed over their head and goggles positioned over their eyes. Following a three-plane gradient echo scan for alignment and brain localization, a shim procedure generated a homogeneous magnetic field. To provide anatomical localization for activation maps, a high-resolution, T1-weighted, 3-D brain scan was obtained using a modified driven equilibrium Fourier transform (MDEFT) sequence ($T_{MD}=1.1$ s, $TR=13$ ms, $TE=6$ ms, $FOV=25.6 \times 19.2 \times 19.2$ cm, $matrix=256 \times 192 \times 96$ pixels, $flip\ angle=20^\circ$). A midsagittal reference scan was obtained to place 30 contiguous 5 mm axial slices extending from the inferior cerebellum to encompass the entire brain. An fMRI scan was then acquired in the coronal view while participants performed the Go/No-Go task using a T2*-weighted gradient-echo planar imaging (EPI) pulse sequence ($TR/TE=3000/30$ msec, $FOV=25.6 \times 25.6$

cm, matrix=64×64 pixels, slice-thickness=4 mm, flip angle=90°). The fMRI data were analyzed using Analysis of Functional NeuroImages (AFNI) software. Preprocessing has been reported in detail elsewhere (Strakowski et al., in press; Fleck et al., in press).

First-level image analysis

Motion correction parameters were included as regressors of no interest in creating individual voxel-wise *t*-statistic maps using an algorithm comparing the actual hemodynamic response to a canonical hemodynamic response function (gamma function). This process generates an estimate of the 'fit coefficient,' i.e., beta weight at each voxel position, which defines the magnitude of the hemodynamic response relative to the average signal intensity. This beta-weight was the primary variable of interest entered into statistical models. Event-related hemodynamic response functions were calculated for correct rejection, omission and commission error trials. Implicitly modeled correct "go" trials provided the baseline against which hemodynamic responses were assessed.

Figure 1a depicts a region-of-interest (ROI) mask created for the VLPFC-subcortical emotional network. The mask was applied to each individual's fMRI activation map to obtain the average activation within each ROI for each trial type. The average activation (average beta-weight) from all voxels within each ROI was extracted from each participant's fMRI results after combining all modeled trial types (correct rejection, omission and commission errors) and used as input to the statistical analysis. The VLPFC-subcortical ROIs included bilateral inferior frontal gyrus (analogous to VLPFC), striatum (caudate and putamen), globus pallidus, thalamus, amygdala, and midline cerebellum. We used the automatic anatomical labeling atlas in AFNI to create these ROIs (Tzourio-Mazoyer et al., 2002), except for the cerebellar ROI, which was created in the vermis as an 8 mm radius sphere centered on coordinate x=5 mm left, y=53 mm posterior, and z=34 mm inferior to the anterior commissure.

Statistical analysis

Data were analyzed using AFNI and SPSS. Significance is reported at $\alpha < 0.05$ and marginal significance at $\alpha < 0.10$ due to the preliminary nature of this study. Group comparisons of demographic and clinical variables were made using one-way ANOVA and independent sample *t*-tests for continuous variables or χ^2 -tests for nominal variables.

The cognitive variable of primary interest was the proportion of commission errors (incorrect responses to non-targets), which is a putative measure of motor impulsivity. Nonparametric signal detection indices of A' , β'' , and hit RT were assessed as secondary outcomes. For each cognitive variable a one-way ANOVA was conducted to examine group differences. In the presence of a significant omnibus effect, follow-up comparisons were made using Tukey's HSD test.

Voxel-wise analyses were performed using subject level *t*-maps as the data for the composite event-related activation maps. Initially, the three study groups were combined to assess the extent to which group-wide spatial activation mirrored that predicted for the *a priori* defined VLPFC-subcortical network. Next, group comparisons were made between the BP-M and HC group and the BP-M and BP-D group, controlling MADRS score differences in the later comparison, to test the imaging hypothesis. Group activation maps were thresholded at voxel-level $p < 0.005$ and 36 contiguous voxels, as determined by Monte-Carlo simulation, for a corrected $p < 0.05$.

The ROI analysis was conducted using the VLPFC-subcortical network mask. Each of 11 ROIs was entered into a one-way ANOVA. In the presence of a significant omnibus result,

follow-up comparisons were made at $p < 0.05$ using Tukey's HSD test, controlling for MADRS score differences in comparing BP-M and BP-D groups.

Results

Demographic and clinical measures

As Table 1 shows, the BP-M, BP-D, and HC groups were matched on all demographic and clinical measures with the exception of premorbid IQ [$F(2,27)=4.32$, $p < 0.05$] and, as expected, Barrett Impulsivity Scale-Version 11 (BIS-11) motor impulsiveness (Patton et al., 1995) [$F(2,27)=8.22$, $p < 0.01$]. Overall manic severity was greater in the BP-M group by definition [$t(17)=11.48$, $p < 0.001$], and depressive symptoms were more severe in the BP-D group [$t(17)=3.14$, $p < 0.01$]. Because our intent was to match the BP-M and BP-D groups on depression severity, MADRS scores were taken as a covariate in subsequent patient group comparisons.

Go/No-Go performance

As Table 1 shows, the HC group made fewer commission errors relative to the patient groups. This impression was confirmed by a marginally significant ANOVA on commission error rate [$F(2,27)=2.94$, $p=0.07$] in which the BP-M group underperformed relative to the HC group ($p=0.09$). The HC group was also significantly better able to discriminate targets from non-targets relative to the patient groups as confirmed by a significant ANOVA on A' [$F(2,27)=10.97$, $p < 0.001$]. Mean comparisons revealed that both BP-M and BP-D groups significantly underperformed relative to the HC group ($p < 0.05$).

Voxel-wise fMRI analysis

Exploratory voxel-by-voxel analyses were conducted to visualize the overall pattern of task-related activation across the entire brain. Figure 1b depicts the composite voxel-wise activation map for the entire study sample. The activation pattern was consistent with that expected for the VLPFC-subcortical network in Figure 1a, with the exception of any significant activation in the amygdala or globus pallidus. Positive activation occurred in bilateral inferior frontal gyrus (BA 47/45) with extension to the insula on the left, right thalamus, and left cerebellum. Negative activation occurred in the left striatum. Positive voxel-wise activation outside the *a priori* defined VLPFC-subcortical network occurred in the right middle frontal gyrus (BA 6), right anterior cingulate (BA 24/32), bilateral inferior parietal lobe (BA 40), and left middle temporal gyrus (BA 21). Extra-network negative activation occurred in the right posterior parahippocampal gyrus (BA 19).

Contrasts of the BP-M group with the HC and BP-D comparison groups revealed a number of structures/regions of differential activation. Relative to the HC group, the BP-M group demonstrated greater activation of the right amygdala (center of mass: $x=-22$, $y=7$, $z=-19$; cluster size=43), right middle frontal gyrus (center of mass: $x=-24$, $y=-34$, $z=3$; cluster size=41), and left medial frontal gyrus (center of mass: $x=10$, $y=32$, $z=-18$; cluster size=37; Brodmann area=11). Relative to the BP-D group, the BP-M group demonstrated greater activation of the left thalamus (center of mass: $x=1$, $y=14$, $z=7$; cluster size=55), left cerebellum (center of mass: $x=48$, $y=34$, $z=-29$; cluster size=45), and right inferior frontal gyrus (center of mass: $x=-55$, $y=-19$, $z=-11$; cluster size=36; Brodmann area=47).

Region-of-interest fMRI analysis

Figure 2 depicts a significant group difference identified in right amygdala only [$F(2,27)=3.55$, $p < 0.05$]. Mean comparisons revealed that this omnibus effect resulted from the HC and BP-M groups deactivating and activating right amygdala, respectively ($p < 0.05$).

Discussion

This study was designed to examine brain activation within the VLPFC-subcortical mood circuit during a Go/No-Go task in patients with BD. We expected that patients in a mixed episode would exhibit greater behavioral deficits and neurophysiological abnormalities relative to healthy and psychiatric comparison groups.

Consistent with previous signal-detection findings in acute BD, both patient groups were less able to discriminate targets from non-targets relative to the healthy group (Fleck et al., 2005; Strakowski et al., 2010). In partial support of the behavioral prediction, the mixed group had difficulty inhibiting prepotent motor responses, resulting in a marginally higher commission error rate than the healthy group. However, the mood state specificity of this effect is questionable considering the null patient group follow-up comparison.

Voxel-wise analysis of the full sample showed general correspondence with ROIs in the *a priori* defined VLPFC-subcortical network, at least unilaterally, confirming this network's role in motor impulsivity. The pattern of decreased striatal and increased frontal lobe and cerebellar activation is consistent with a brain circuit thought to represent the affective response to Go/No-Go error processing (Stevens et al., 2008). Parietal lobe activation outside the VLPFC-subcortical network *per se* may represent a complimentary posterior attention system (Posner and Peterson, 1990) previously demonstrated in fMRI studies of attention in healthy (Adler et al., 2001), euthymic (Strakowski et al., 2004) and manic (Fleck et al., in press) participants alike.

In voxel-wise comparisons, the mixed group overactivated the VLPFC-subcortical network relative to healthy and patient comparison groups. Regions of increased activation included amygdala and OFC (BP-M>HC), and VLPFC, thalamus and cerebellum (BP-M>BP-D). Impulsivity in primary mania has been previously associated with blunted rather than increased VLPFC activation, but this is in the context of normal Go/No-Go accuracy (Altshuler et al., 2005; Mazzola-Pomietto et al., 2009). The present finding of greater VLPFC and OFC activation in mixed mania may suggest a connection between response non-suppression (motor impulsivity) and failure constraining primary emotional brain centers (especially amygdala, OFC, and VLPFC). Over-activation of right amygdala in the ROI analysis provides additional support for this interpretation, but it is still speculative considering the lack of group activation differences within inferior frontal lobe ROIs. Functional connectivity studies are necessary to determine the temporal relationship between amygdala and frontal lobe activation to specify whether frontal activation actually constrains amygdala or is simply a cortical representation of limbic activation.

These results should be interpreted in light of certain study limitations. Foremost, the sample size was modest and may provide insufficient statistical power to detect certain effects. It is generally accepted that group sizes <10 are suboptimal in fMRI studies (Friston et al., 1999). Additionally, the majority of participants with BD were receiving medications, potentially impacting the findings. The small number of unmedicated patient participants limited meaningful sub-analysis however. Finally, although our intent was to match the patient subgroups on depressive symptom severity, mean MADRS differences necessitated statistical control instead.

To our knowledge this is the first fMRI study examining neurophysiological functioning in mixed episode BD. Higher commission error rates may suggest increased vulnerability to impulsivity during mixed episodes. Moreover, the distinct pattern of greater brain activation in mixed mania may indicate a connection between behavioral impulsivity and a failure of neurophysiological "inhibition," particularly in the right amygdala. Taken together, these results provide preliminary evidence for functional abnormalities within a VLPFC-

subcortical emotional network during impulsive motor responding in mixed mania. Functional brain variations during motor impulsivity in mixed episodes, even in relation to depressed episodes, might serve as proxy state markers of risk taking behaviors.

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Figure 1.

(a) Regions of a VLPFC-subcortical emotional network mask overlaid on T1-weighted anatomic image. Colors represent eleven regions of interest including midline cerebellum (orange), bilateral amygdala (red), bilateral inferior frontal gyrus (light blue), bilateral striatum (green), bilateral globus pallidus (pink), and bilateral thalamus (dark blue). (b) Composite functional brain maps of Go/No-Go activation overlaid on T1-weighted anatomic image for the full sample (Healthy Control, Bipolar Depressed, and Bipolar Mixed). Significant activation is defined as threshold $p < 0.005$ with voxel cluster size ≥ 36 contiguous voxels to control for multiple comparisons (corrected $p < 0.05$). Orange and blue scales represent activation and deactivation, respectively, relative to a zero activation baseline. The left and right sides of the image correspond to the left and right sides of the brain.

Figure 2.

Regional activation within the right amygdala in 10 Healthy Control, 10 Bipolar Depressed and 8 Bipolar Mixed participants while performing the Go/No-Go task (0.005 raw signal = approx. 0.1 percent signal change). Significant one-way ANOVA [$F(2,25)=3.55$, $p<0.05$]. Significant pair-wise comparison Bipolar Mixed > Healthy Control ($p<0.05$). Error bars represent standard error.

Table 1

Demographic and clinical characteristics of the study groups

Variable	Control (n=10)	Mixed (n=8)	Depressed (n=10)	p<
<u>Demographic/Clinical</u>				
Age, yrs (SD)	33 (8)	30 (8)	34 (10)	Ns
Sex, female, n (%)	8 (80)	6 (67)	5 (50)	Ns
Race, white, n (%)	10 (100)	8 (89)	9 (90)	Ns
Education, yrs (SD)	15 (2)	14 (3)	14 (2)	Ns
ANART premorbid IQ (SD) ^a	115 (8)	106 (9)	105 (8)	0.05
BIS motor impulsiveness (SD)	18 (3)	25 (5)	25 (5)	0.01
<u>Patient Characteristics</u>				
Prior episodes, n (SD)	--	55 (76)	48 (68)	Ns
Length of episode, wks (SD)	--	3 (1)	3 (2)	Ns
YMRS (SD)	--	24 (2)	9 (3)	0.001
MADRS (SD)	--	22 (5)	29 (6)	0.01
SAPS (SD)	--	2 (1)	1 (3)	Ns
CGI (SD)	--	3 (1)	3 (1)	Ns
<u>Cognitive Performance</u>				
Proportion commission errors (SD)	0.25 (0.14)	0.40 (0.10)	0.37 (0.16)	0.10
Perceptual sensitivity, A' (SD)	0.82 (0.08)	0.70 (0.08)	0.62 (0.13)	0.001
Response bias, β'' (SD)	0.01 (0.16)	-0.03 (0.07)	0.01 (0.06)	Ns
Hit reaction time, ms (SD)	459 (20)	443 (23)	442 (36)	Ns

ANART = American Modification of the National Adult Reading Test; BIS motor impulsivity = Barrett Impulsivity Scale Version 11 – motor impulsivity subscale; YMRS = Young Mania Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; SAPS = Scale for Assessment of Positive Symptoms; CGI = Clinical Global Impression scale.